



TITLE:

# A novel diagnostic criterion for lymph node metastasis in cervical cancer using multi-detector computed tomography.

AUTHOR(S):

Yamanoi, Koji; Matsumura, Noriomi; Kido, Aki; Baba, Tsukasa; Hamanishi, Junzo; Yamaguchi, Ken; Yoshioka, Yumiko; Taleb, Hisham Abou; Togashi, Kaori; Konishi, Ikuo

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1 Original Article

2 **A novel diagnostic criterion for lymph node metastasis in cervical cancer using**  
3 **multi-detector computed tomography**

4

5 Koji Yamanoi, MD<sup>a</sup>, Noriomi Matsumura, MD, PhD<sup>a†</sup>, Aki Kido, MD, PhD<sup>b</sup>, Tsukasa Baba,  
6 MD, PhD<sup>a</sup>, Junzo Hamanishi, MD, PhD<sup>a</sup>, Ken Yamaguchi, MD, PhD<sup>a</sup>, Yumiko Yoshioka, MD,  
7 PhD<sup>a</sup>, Hisham Abou Taleb, MD<sup>a</sup>, Kaori Togashi, MD, PhD<sup>b</sup>, Ikuo Konishi, MD, PhD<sup>a</sup>

8

9 <sup>a</sup> Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine

10 <sup>b</sup> Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate  
11 School of Medicine

12

13 †Corresponding Author

14 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan

15 Tel: +81-75-751-3269

16 Fax: +81-75-761-3967 (facsimile)

17 Email: [noriomi@kuhp.kyoto-u.ac.jp](mailto:noriomi@kuhp.kyoto-u.ac.jp)

18

19   **Keywords:** cervical cancer, lymph node metastasis, multi-detector computed tomography

20   (MDCT), neoadjuvant chemotherapy (NAC)

21

22    **ABSTRACT**

23    **Objectives:** The sensitivity of the current 10 mm cut-off diameter that is used to diagnose  
24    lymph node (LN) metastasis is too low. This is the first study to develop a new criterion to  
25    diagnose LN metastasis in a region-by-region manner using multi-detector computed  
26    tomography (MDCT).

27    **Methods:** 1) The short-axis diameter of the LNs in MDCT images from 1-mm slices  
28    obtained immediately prior to surgery was compared with the pathological diagnosis in 78  
29    uterine cervical cancer patients undergoing primary surgery. For the region-by-region  
30    analysis, we divided para-aortic and pelvic spaces into 13 regions. 2) In 28 cases in which  
31    patients received neoadjuvant chemotherapy (NAC) followed by surgery, we compared  
32    MDCT images before and after NAC.

33    **Results:** 1) The optimal cut-off in the region-by-region analysis was 5 mm, yielding 71%  
34    sensitivity and 79% specificity. 2) NAC significantly decreased LN size ( $p<0.0001$ ). NAC  
35    decreased the number of swollen LN regions ( $>5$  mm) from 51% (81/158) to 26% (41/158).

36    **Conclusions:** The new criterion developed using MDCT could be effective for accurately  
37    assessing LN status. It also facilitates the assessment of NAC efficacy regarding the  
38    eradication of LN metastases.

39



## INTRODUCTION

Cervical cancer is the second most common gynecologic malignancy in the world [1].

In addition to surgery and radiotherapy, neoadjuvant chemotherapy (NAC) followed by surgery has been used to treat locally advanced cervical cancer [2]. Because the prognosis of patients with cervical cancer depends largely on lymph node (LN) metastasis [3–5], it is important to assess the LN status accurately before starting treatment.

Based on studies comparing the size of the LNs in images and pathological diagnoses, a 10 mm short-axis diameter became the currently accepted cut-off in both clinical practice and clinical trials [6–8]. However, the sensitivity of this conventional criterion has been reported to be as low as 25% [9]. Furthermore, previous studies have generally predicted the presence of LN metastases in the patient without describing the location. In the present study, we conducted a detailed, region-by-region analysis to generate a new criterion that could identify region-specific, swollen LNs. The use of our criterion could lead to the improvement of individualized treatments.

In conducting the detailed analysis of LN status, the width of the slices, 7 mm in conventional CT and 5 mm in MRI, was considered to be a key limitation [7]. We therefore used a multi-detector CT (MDCT) scanner, which allowed one mm slice images [10, 11].

57 Using MDCT, we successfully generated a new criterion to diagnose LN metastasis. Using

58 the new criterion, we were able to examine the efficacy of NAC in eradicating LN metastases

59 in a region-by-region manner for the first time.

60

## 61 MATERIALS AND METHODS

### 62 Assessment of MDCT images

#### 63 *Patients*

64 Patients with stage IA2 to IIB cervical cancer who were being treated in our  
65 department were retrospectively analyzed. Staging was performed according to the  
66 Classification of International Federation of Gynecology and Obstetrics (FIGO, 1994) [12].  
67 With the written consent of each patient, and under the approval of the ethics committee, we  
68 initiated the MDCT study in January 2007: 106 patients underwent MDCT examination  
69 within two weeks before surgery; 78 patients underwent primary surgery; and the remaining  
70 28 patients received NAC followed by surgery. In Table 1, we show the number of patients  
71 arranged according to their cancer stage.

72 Lymphadenectomy was performed during all of the surgeries, and we resected LNs  
73 separately in a region-by-region manner and made pathological diagnoses for each sample.

#### 74 *NAC regimen and indication*

75 Because squamous cell carcinoma (SCC) was more sensitive than adenocarcinoma to  
76 chemotherapy in our preliminary analysis, we administered NAC primarily in stage  
77 IB2/IIA/IIB SCC cases (Table 1). An intravenous infusion of irinotecan (CPT-11) ( $60 \text{ mg/m}^2$

78 on days one and eight) and nedaplatin (NDP) (80 mg/m<sup>2</sup> on day one) was administered.

79 Cycles were repeated every 21 days. In total, we conducted two cycles of NAC.

80 *Surgical procedures and the definition of LN location*

81 Pelvic lymphadenectomy was conducted in association with type III radical  
82 hysterectomy. The surgical procedure has been reported previously [13].

83 Para-aortic lymphadenectomy was performed when a metastatic pelvic LN was found  
84 after the intraoperative pathological diagnosis of frozen sections or when the surgeon found it  
85 necessary. LNs and their surrounding tissue were removed from the bifurcation of the  
86 common iliac artery to either the inferior mesenteric artery (IMA) or the level of the renal  
87 vein.

88 *MDCT protocol*

89 The MDCT examination was performed using one of three 64-detector-row CT  
90 scanners (Aquilion, Toshiba Medical Systems, Otawara, Japan) or a 16-detector-row CT  
91 scanner (Aquilion, Toshiba Medical Systems, Otawara, Japan). Patients were placed in the  
92 supine position, and the whole abdomen and pelvis were scanned. Image data were acquired  
93 with a 7 mm slice thickness, using a 64 × 0.5 mm (64-detector-row CT) or 16 × 1.0 mm  
94 (16-detector-row CT) beam collimation, a 500 msec rotation time, and a 120 kVp and 27.5

mm (64-detector-row CT) or 14.9 mm (16-detector-row CT) table feed per rotation. The acquired images were used to generate images with 1 mm slice thickness. All dual-phase contrast-enhanced CT images with a single breath-hold were obtained at 90 seconds following the intravenous injection of 100 ml of 300 or 350 mg/ml non-ionic contrast medium (Iomeron<sup>®</sup>350, Eisai, Tokyo, Japan; Iopamiron<sup>®</sup>300, Bayer HealthCare, Osaka, Japan; or Omnipaque<sup>®</sup>300, Daiichi-Sankyo, Tokyo, Japan) at a rate of 2.5 ml/sec using an automatic injector.

Because our MDCT procedure is the same as previously reported [14], the estimated radiation dose to the whole abdomen was approximately 10mSv. The noise of the images with 1mm thickness was greater than those with 7mm thickness. However, there was no difficulty in evaluating length of LNs, especially in MDCT images with contrast enhancement.

#### *Evaluation of LNs by MDCT*

The evaluation of LNs using the MDCT images of 1 mm-thick slices was performed independently by a radiologist (AK) who specializes in the field of gynecology and by a gynecologic oncologist (KY). The size of each LN, measured independently by AK and KY to the first decimal place, was determined by consensus of them.

## 112 *Region-by-region analysis*

113           Most previous studies have been conducted in patient-by-patient manner. In this  
114 study, we aimed to analyze more closely. Because it is unfeasible to compare each LN  
115 detected in MDCT images with LN detected in operation in node-by-node manner, we  
116 employed a region-by-region analysis. In a previous study, the pelvic and para-aortic spaces  
117 were divided into five regions prior to conducting a region-by-region analysis [9]. In the  
118 present study, we divided them into 13 regions (Supplementary Figure 1) to conduct a more  
119 detailed analysis. We determined the size of the largest LN in each region, termed the  
120 regional LN (Reg-LN), and compared it with the pathological diagnosis of LN metastasis in  
121 each region. We should note that even if LN metastasis existed in a region, the Reg-LN might  
122 not be the involved LN. Receiver operating characteristic (ROC) curve were drawn to  
123 determine the optimal cut-off size. For the development of the new criterion, we analyzed  
124 only the primary operation cases and excluded the NAC cases.

## 125 *Estimate of the efficacy of NAC in eradicating LN metastases using MDCT images*

126           In patients who received NAC, we performed the MDCT examination before and  
127 after NAC and compared the results. Using the new criterion for determining the swollen  
128 Reg-LN, we estimated the efficacy of NAC in eradicating LN metastasis.

129

130 *Statistical methods*

131           We used t-tests to compare the parametric values between two groups and one-way  
132 ANOVA for three groups. Paired t-tests were used for the paired analysis. To analyze the  
133 distribution in a 2x2 table, Fisher's exact test was employed. To analyze the distribution in a  
134 larger table, the chi-square test was used. We considered a value of  $p < 0.05$  to be a significant  
135 difference.

136

## 137     **RESULTS**

### 138     **Detection of LNs in 1 mm slice images from MDCT.**

139             A total of 4,765 LNs were pathologically identified within 980 regions from 106  
140     patients, whereas the total number of visible LNs in the MDCT images was 800. Thus, the  
141     detection rate of LNs by MDCT was 17% (800/4,765). The most difficult LN to detect was  
142     the presacral LN (6%), whereas the easiest was the left common iliac LN (46%) (Figure 1a).  
143     Only seven of the 800 visible LNs in the MDCT images were over 10 mm in diameter.

144             Among 980 regions from 106 patients, 563 (57%) regions showed one or more visible  
145     LNs in the MDCT images. Metastases were identified pathologically in 133 LNs within 80  
146     regions from 33 patients. Sixty of these 80 (75%) regions showed one or more visible LNs in  
147     the MDCT images (Figure 1b). The detection rate was significantly higher in the metastatic  
148     regions than in the non-metastatic regions ( $p=0.006$ ) (Figure 1b). In the following analyses,  
149     the largest LN in each region was defined as the Reg-LN.

### 150     **Development of a new criterion to diagnose LN metastasis.**

151             We compared the size of the Reg-LN identified by MDCT with the presence or  
152     absence of a pathologically involved LN in 410 regions from 71 patients who underwent  
153     primary surgery and in whom the Reg-LN could be detected in the MDCT images. Statistical



analysis using the ROC curve is difficult when the number of metastasis-positive cases is less than five. Only the external iliac and obturator regions were positive for metastasis in five or more patients. Thus, we analyzed the Reg-LNs of the obturator region, external iliac region, and the other regions separately. In all three groups, the size of the Reg-LN was significantly larger in the LN regions containing metastases than in the non-metastatic regions; the mean was 7.9 in the metastatic case vs. 4.0 mm in the non-metastatic case in the external iliac ( $p<0.0001$ ), 6.6 vs. 3.9 mm in the obturator ( $p<0.0001$ ), and 5.1 vs. 3.8 mm in the other regions ( $p=0.003$ ) (Figure 2a). The variation in the size of the Reg-LNs in these three groups was not significant in either metastatic or non-metastatic regions (Figure 2a). The optimal cut-off sizes determined by the ROC curves in the external iliac, obturator, and other regions were 4.9, 5.3, and 5.1 mm, respectively (Figure 2b). Based on these results, 5 mm was selected as the cut-off size for all types of LN regions.

We then analyzed the Reg-LNs from all regions. The size of the Reg-LNs was significantly larger in the LN regions containing metastases than in the regions without metastases: mean 6.4 mm vs. 3.9 mm ( $p<0.0001$ ) (Figure 3a). Based on the ROC curve, the optimal cut-off size to diagnose a LN metastasis was 4.7 mm ( $AUC = 0.80$ , Figure 3b). In the region-by-region analysis, we decided the closest whole number, 5 mm, as the cut-off for

clinical use. When the 5 mm cut-off was used, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value were 70, 79, 27, and 96%, respectively.

Next, we divided all cases into SCC and non-SCC to examine the influence of histological differences on the detection of LN metastasis. In both SCC and non-SCC patients, the size of the Reg-LN was significantly larger in the LN regions with metastases than in the non-metastatic regions: the mean in SCC was 7.1 vs. 4.0 mm and in non-SCC was 6.0 vs. 3.7 mm ( $p < 0.0001$ ) (Figure 3a). The size of the Reg-LN in non-metastatic LN regions was larger in SCC compared with non-SCC, but the difference was small (Figure 3a). The optimal cut-off determined by the ROC curve was 5.4 mm in SCC and 4.7 mm in non-SCC cases (Figure 3c). Thus, 5 mm, the closest whole number, was again selected for use in both histological subtypes.

We also evaluated the conventional 10 mm cut-off. In the primary surgery cases, only four of all the visible LNs in the MDCT images were over 10 mm in diameter (Figure 2a). We found that the conventional cut-off of 10 mm was far from the optimal cut-off based on the ROC analyses (Figure 2b, 3b, 3c). In addition, we randomly divided our data (primary surgery cases, region-by-region data) into three groups and conducted ROC analyses independently, thus generating cut-off values of 4.9, 5.0 and 5.3 (95% CI; 4.55-5.58, data not

shown). We therefore concluded that the conventional 10 mm cut-off is statistically inappropriate in MDCT images.

#### **Assessment of NAC efficacy on metastatic LNs in cervical cancer.**

We analyzed 153 Reg-LNs from 28 patients who underwent NAC followed by surgery using the MDCT images taken just before surgery. As in the primary surgery cases, the size of the Reg-LN was significantly larger in the metastatic regions than in the non-metastatic regions: the mean was 7.4 vs. 3.9 mm ( $p < 0.0001$ ) (Figure 4a). The size of the Reg-LN in the metastatic and non-metastatic LN regions was the same within the NAC and primary surgery groups (Figure 4a). Similar to the primary surgery cases (Figure 4b), the optimal cut-off determined by the ROC curve was 4.7 mm in NAC cases (AUC = 0.83, Figure 4c).

Next, we examined the size change of LNs after NAC. For this analysis, node-by-node comparison was performed. First, we compared the size of all visible 328 LNs individually between before and after NAC. NAC significantly decreased the size of LNs from 5.1 to 3.5 mm ( $p < 0.0001$ ) (Figure 5a): this is the reduction in the average size of all visible LNs. For Reg-LNs, we found 158 Reg-LNs in MDCT images before NAC. The size of these 158 Reg-LNs was also significantly decreased by NAC from 5.9 to 4.3 mm

205 (p<0.0001) (Figure 5b). Using the cut-off of 5 mm, 80 out of 158 Reg-LNs (51%) were 5 mm  
206 or greater in diameter before NAC. After NAC, the number of Reg-LNs that were 5 mm or  
207 greater was significantly decreased to 41 (p<0.0001, 26%) (Figure 5c). Of these 41 regions,  
208 13 (32%) had LN metastases based on their pathology. Among 78 regions that were less than  
209 5 mm in diameter before NAC, a LN metastasis was identified in only 1 region (1%) after  
210 NAC.

211 In addition to the analysis of MDCT images, we reviewed the medical records of  
212 cervical cancer cases that were treated in our hospital between 1999 and 2011. In accordance  
213 with the MDCT analysis, we found that NAC decreased the frequency of LN metastasis  
214 (Supplementary text, Supplementary Figure 2b).

215

216 **DISCUSSION**

217           The main objective of this study was to generate a new and more reliable criterion to  
218   diagnose LN metastasis pre-operatively. We also evaluated the efficacy of NAC in  
219   eradicating LN metastasis using the newly developed criterion because NAC has the potential  
220   to eradicate LN and distant metastases [2, 15, 16].

221           CT and MRI have been widely used to diagnose LN metastasis [17, 18]. In  
222   conventional CT or MRI images of 5-7 mm slices, 10 mm is used as the conventional cut-off  
223   for the short-axis diameter in the diagnosis of swollen LNs as potential metastases. However,  
224   only seven of 800 visible LNs in the MDCT images were over 10 mm in diameter in this  
225   study (data not shown). Therefore, the conventional cut-off of 10 mm is not effective in  
226   clinical practice. The conventional cut-off is used because of the limitations of conventional  
227   CT, which cannot reproducibly measure an object smaller than 10 mm in diameter in 5-7 mm  
228   slices [7].

229           MDCT is a new form of CT technology and that has an increased speed of CT image  
230   acquisition [18]. In addition, MDCT provides more information than CT without increasing  
231   cost, examination time, or exposure dose depending on how it is protocolled. Although there  
232   are reports demonstrating the use of MDCT to diagnose LN metastasis in gastric,

233 oesophageal, breast and pancreatic cancer [10, 11, 20-22], to the best of our knowledge, this  
234 is the first report on the use of MDCT in a gynecological cancer.

235 In previous studies that examined the diagnostic rate for LN metastasis,  
236 patient-by-patient analysis was used to compare the size of the largest LN in a patient with  
237 the pathological diagnosis of the LN metastasis, without describing the location of LN  
238 metastasis. However, to consider individually the extent of the lymphadenectomy and field of  
239 radiotherapy, a diagnosis of not only the presence of a LN metastasis but also the location(s)  
240 of the LN metastasis is essential. Accordingly, we determined that the cut-off should be  
241 ascertained using region-by-region analysis.

242 Our findings suggested that 5 mm was the most appropriate cut-off for clinical  
243 practice. In addition, a cut-off of 5 mm using MDCT was reproducible regardless of the  
244 location or pathological subtype of the tumor (Figures 3b, 3c, 4c). The ROC analyses clearly  
245 showed that a cut-off of 10mm is not appropriate.

246 Using historical analysis of stage IB2/IIA cases, we found that the frequency of LN  
247 metastasis in NAC cases was significantly lower than in primary surgery cases  
248 (Supplementary Figure 2b). This result is consistent with previous reports that the frequency  
249 of LN metastasis is lower in patients who undergo NAC [15, 16]. In our analysis,

250 approximately half of the Reg-LNs that were 5 mm or larger shrank to less than 5 mm after  
251 NAC (Figure 5c). Although shrinkage of LNs does not necessary mean anti-tumor effect  
252 against involved LNs, this study shows a substantial number of involved LNs might have  
253 been cured by NAC. Ours is the first study to report the precise change in LN size due to  
254 NAC; however, further studies are required to confirm whether NAC is effective against the  
255 LN metastasis of cervical cancer.

256 In this study, using 1mm slice images, we tried evaluating LN size as closely as  
257 possible in region-by-region manner, but there are still some limitations. The largest LN in an  
258 involved region may not always be the involved LN. To compare the preoperative image with  
259 the pathological diagnosis in node-by-node manner, data accumulated from image-guided  
260 surgery, currently used for gastric or liver cancer [23, 24] are necessary. Although the  
261 detection rate of at least one LN in a region was increased when involved LNs exist, the  
262 detection rate was still 75 %, not 100% (Figure 1b). Among operable cervical cancer patients,  
263 PPV of 5 mm cut-off was only 27% although PPV is thought to be higher in advanced cases  
264 where operation is impossible and radiotherapy is indicated.

265 Regardless, the results of our study should have an enormous impact on clinical  
266 practice. We consider LNs of 5 mm or larger to be potentially metastatic. We hope this result

267 would be validated in a prospective study with a large number of cases and node-by-node  
268 surgery with imaging analysis.

269 In conclusion, we suggested an optimal cut-off of 5 mm in MDCT images for the  
270 diagnosis of metastatic LNs within an LN region. This novel diagnostic criterion would  
271 improve the individualized treatment of cervical cancer patients. In the future, clinical trials  
272 should be performed to investigate whether this strategy could improve the prognosis of  
273 cervical cancer patients.

274

275 Conflict of Interest Statement: All authors declare that they have no conflicts of interest.

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278



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347

## 348 **FIGURE LEGENDS**

349 **Figure 1.** Detection of LNs in MDCT images. a) The number of detected LNs by MDCT is  
350 indicated by a black box. Pathologically detected LNs are indicated by the sum of the  
351 detected and undetected LNs. The distribution was statistically significant ( $p < 0.0001$ ,  
352 chi-square test). PAN: para-aortic LN region; IMA: inferior mesenteric artery; Bif: aortic  
353 bifurcation; L: left; R: right. b) The detection rate of Reg-LNs was significantly higher in the  
354 involved regions (pN1) than in the uninvolved regions (pN0) ( $p = 0.006$ ).

355 **Figure 2.** Region-by-region analysis of LNs. a) Each dot indicates the size of the Reg-LN.  
356 Red dots indicate size of involved Reg-LNs and tiny black dots indicate size of uninvolved  
357 Reg-LNs. Black bar indicates the mean size. Ext: external iliac region; Obt: obturator region;  
358 Others: all other regions. One-way ANOVA was used for the statistical analysis. b) ROC  
359 curves based on the size of the Reg-LN and the presence of the LN metastasis. The gray  
360 arrowhead indicates the optimal cut-off based on the ROC curves. Note that the 10mm  
361 cut-off indicated by the black arrowhead is away from the optimal cut-off based on the ROC  
362 analysis.

363 **Figure 3.** Region-by-region analysis of all Reg-LNs among different histological subtypes. a)  
364 Each dot indicates the size of the Reg-LN. Red dots indicate size of involved Reg-LNs and

365 tiny black dots indicate size of uninvolved Reg-LNs. Black bar indicates the mean size. To  
366 detect the association of all Reg-LNs with the different histological subtypes present in the  
367 three groups, one-way ANOVA was performed. b) ROC curves are based on the size of the  
368 Reg-LN and the presence of the LN metastases. c) ROC curve analyses were conducted by  
369 dividing the cases into different histological subtypes. The gray arrowhead indicates the  
370 optimal cut-off based on the ROC curves. Note that the 10mm cut-off indicated by the black  
371 arrowhead is away from the optimal cut-off based on the ROC analysis.

372 **Figure 4.** Region-by-region analysis for primary surgery cases and NAC cases, and the effect  
373 of NAC based on the analysis of MDCT images. a) Each dot indicates the size of the Reg-LN.  
374 Primary: primary surgery; pN0: no LN metastasis; pN1: LN metastasis; NS: not statistically  
375 significant. b) ROC curves are based on the size of the Reg-LN and the presence of the LN  
376 metastasis in all primary surgery cases. The gray arrowhead indicates the optimal cut-off  
377 based on the ROC curves. c) ROC curve representing only the NAC cases. The cut-off in the  
378 NAC cases was 4.7 mm.

379 **Figure 5.** Effect of NAC according to MDCT images. a) Changes in all LN sizes that were  
380 visible before NAC. They shrank significantly after NAC ( $p<0.0001$ ). b) Changes in all  
381 Reg-LN sizes by NAC. They also shrank significantly ( $p<0.0001$ ). c) NAC's effect of

382 decreasing the proportion of regions with a LN larger than 5 mm (black bar). Red boxes  
383 indicate regions with LN metastasis. NAC decreased the number of regions with LNs larger  
384 than 5 mm from 80 to 41. In the 41 regions that had Reg-LNs larger than 5mm after NAC, we  
385 found 13 (32%) involved regions; in the 117 regions that had Reg-LNs smaller than 5 mm  
386 after NAC, we found 6 (5%) involved regions.

387 **Supplementary Figure 1.** We divided para-aortic and pelvic lymph nodes into 13 regions to  
388 compare pre-operative images with the pathological diagnosis. a) para-aortic lymph nodes,  
389 from IMA to renal vein; b) para-aortic lymph nodes, from bifurcation to IMA; c) right  
390 common iliac lymph nodes; d) left common iliac lymph nodes; e) presacral lymph nodes; f)  
391 right external iliac lymph nodes; g) right internal iliac lymph nodes; h) left internal iliac  
392 lymph nodes; i) left external iliac lymph nodes; j) right superficial inguinal lymph nodes; k)  
393 lymph nodes in the right obturator fossa (obturator, carinal, uterine artery, and deep inguinal  
394 lymph nodes); l) lymph nodes in the left obturator fossa; m) left superficial inguinal lymph  
395 nodes.

396 **Supplementary Figure 2.** a) Changes in the treatment modality for SCC cases in our  
397 hospital. For stage IB2/IIA SCC cases, we predominantly performed the primary operation  
398 before 2006 and the NAC after 2007. b) NAC decreased the frequency of LN metastasis in



399 stage IB2/IIA SCC patients. c) Among IB2/IIA cases, NAC-treated cases showed a tendency  
400 toward better survival compared with the primary operation cases, although this result was  
401 not statistically significant.  
402

403 **TABLE**

404

405 Table 1. Number of patients multi-detector CT image was analyzed.

406

Stage	SCC	Non-SCC	Total
IA	4	3	7
IB1	32	20	52
IB2	10 (7)	4 (1)	14 (8)
IIA	4	1	5
IIB	23 (19)	5 (1)	28 (20)
Total	73 (26)	33 (2)	106 (28)

407 ( ); NAC cases.

408

Figure 1

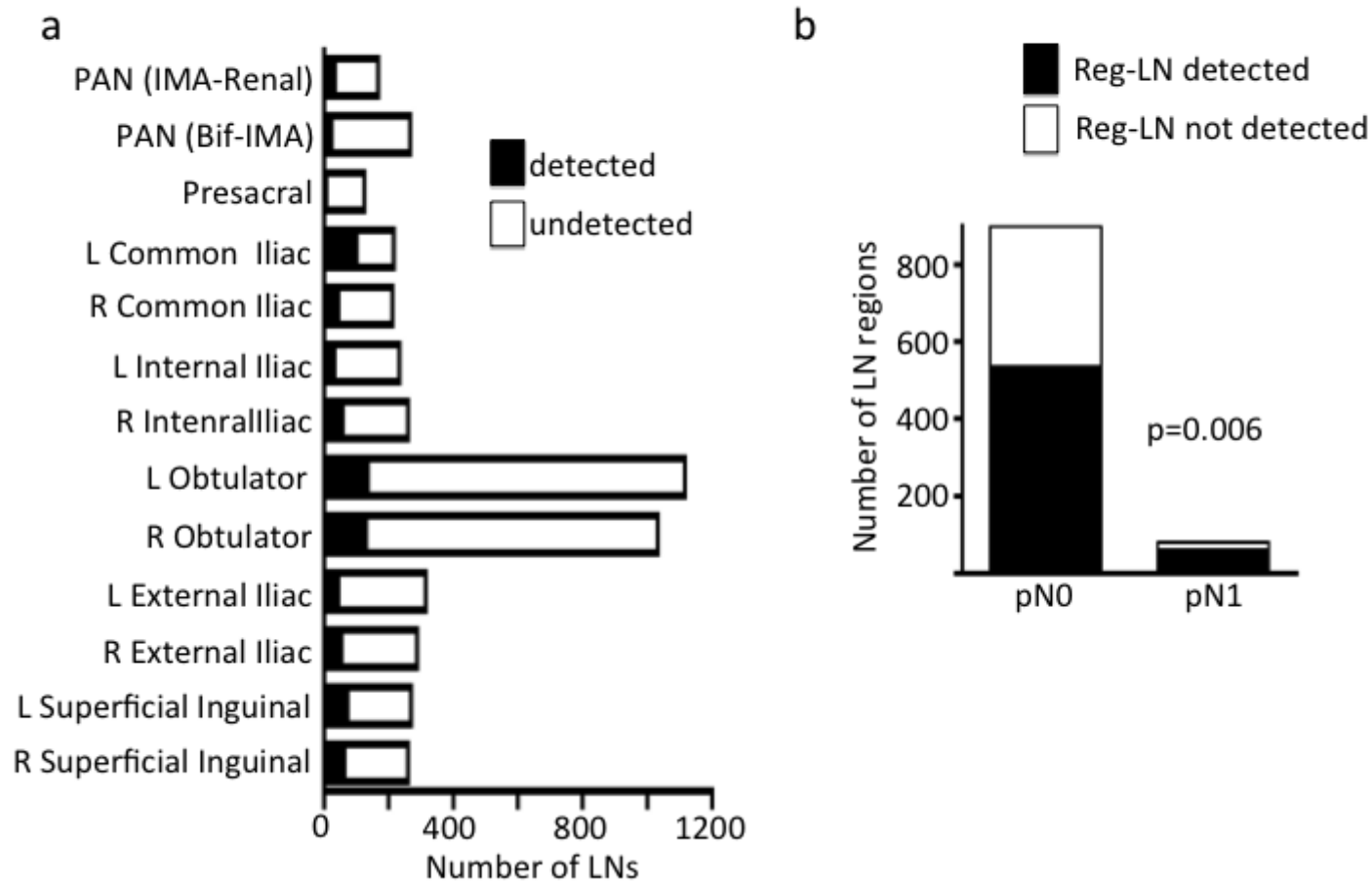
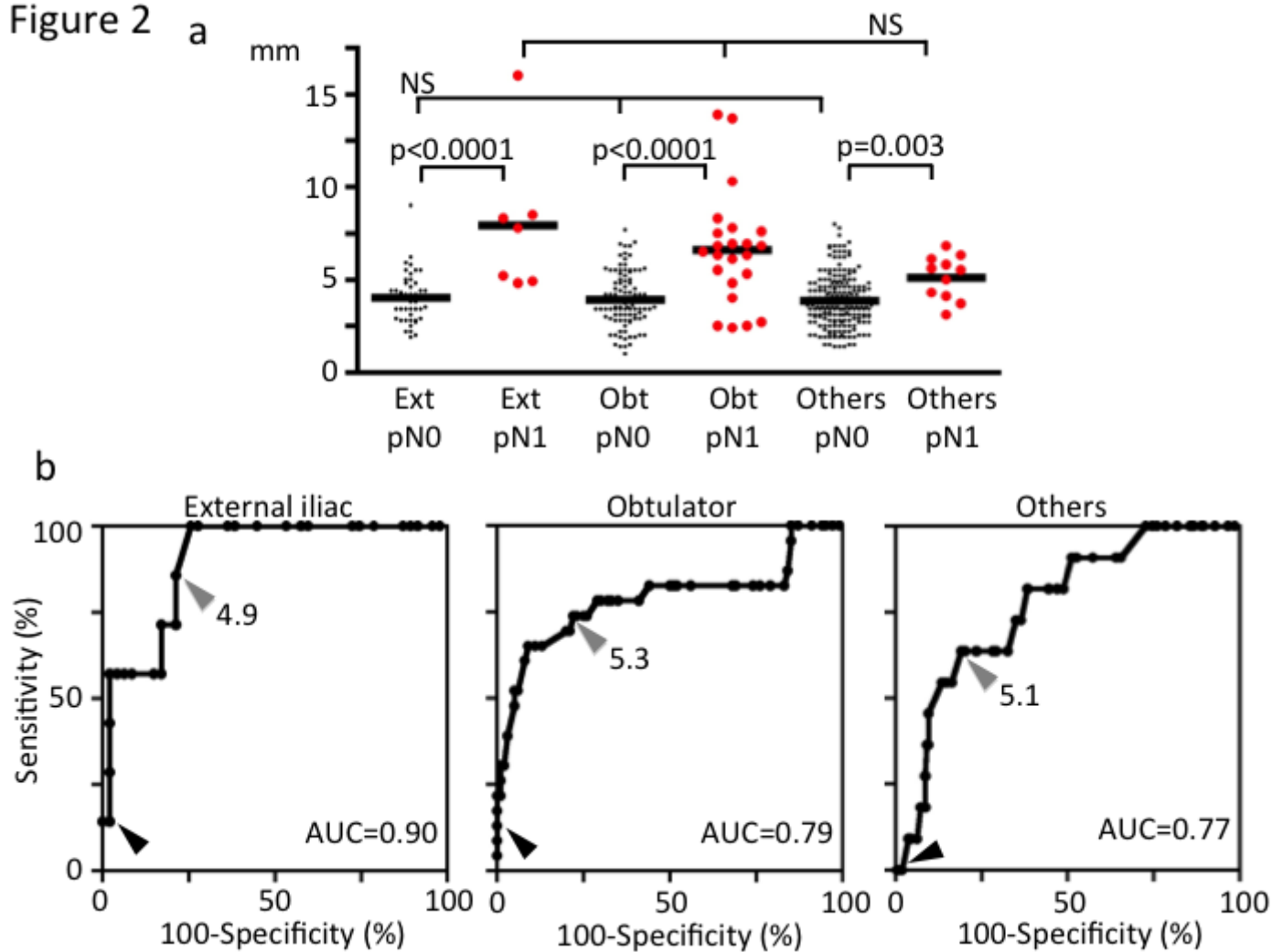


Figure 2



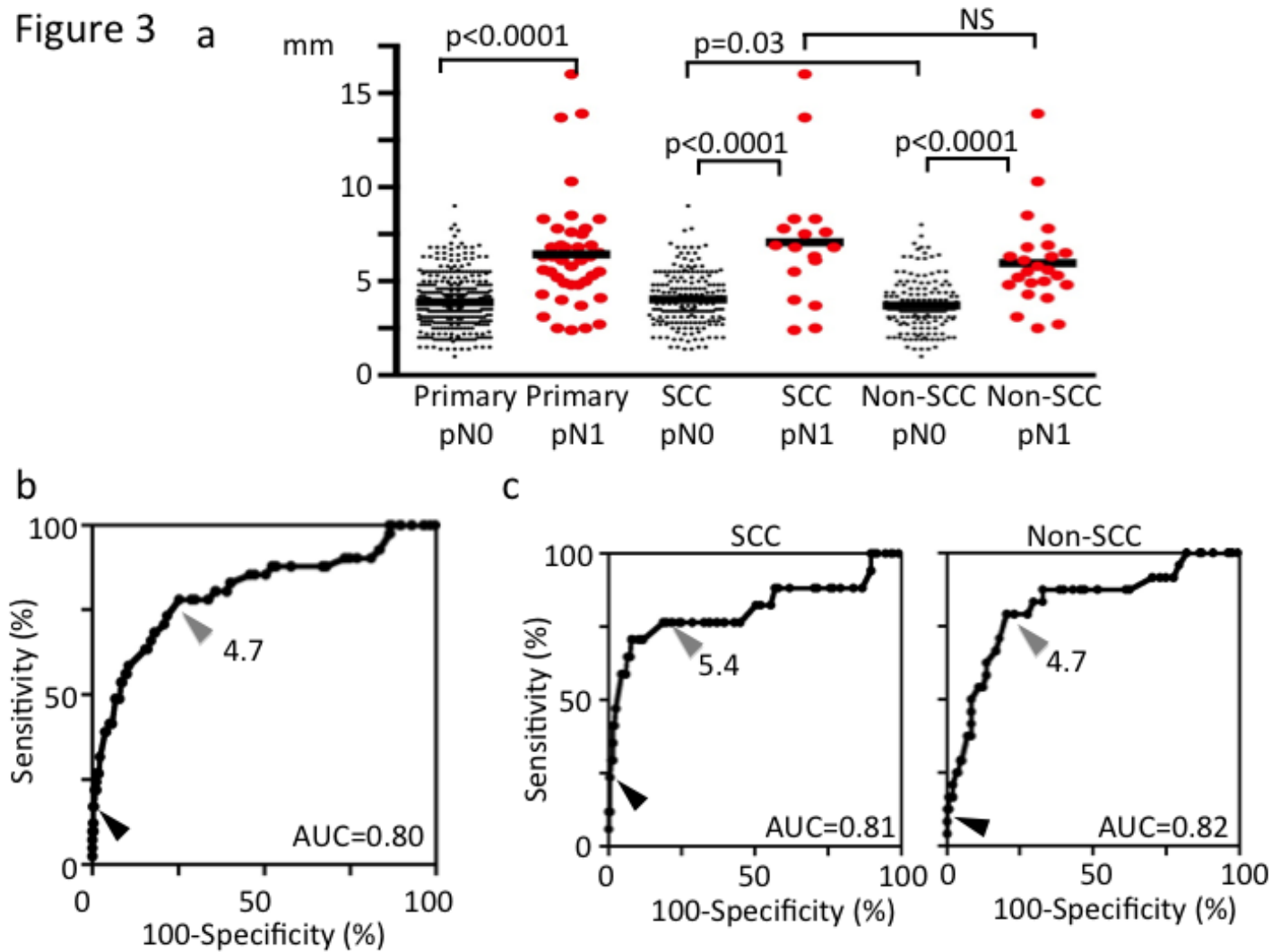


Figure 4

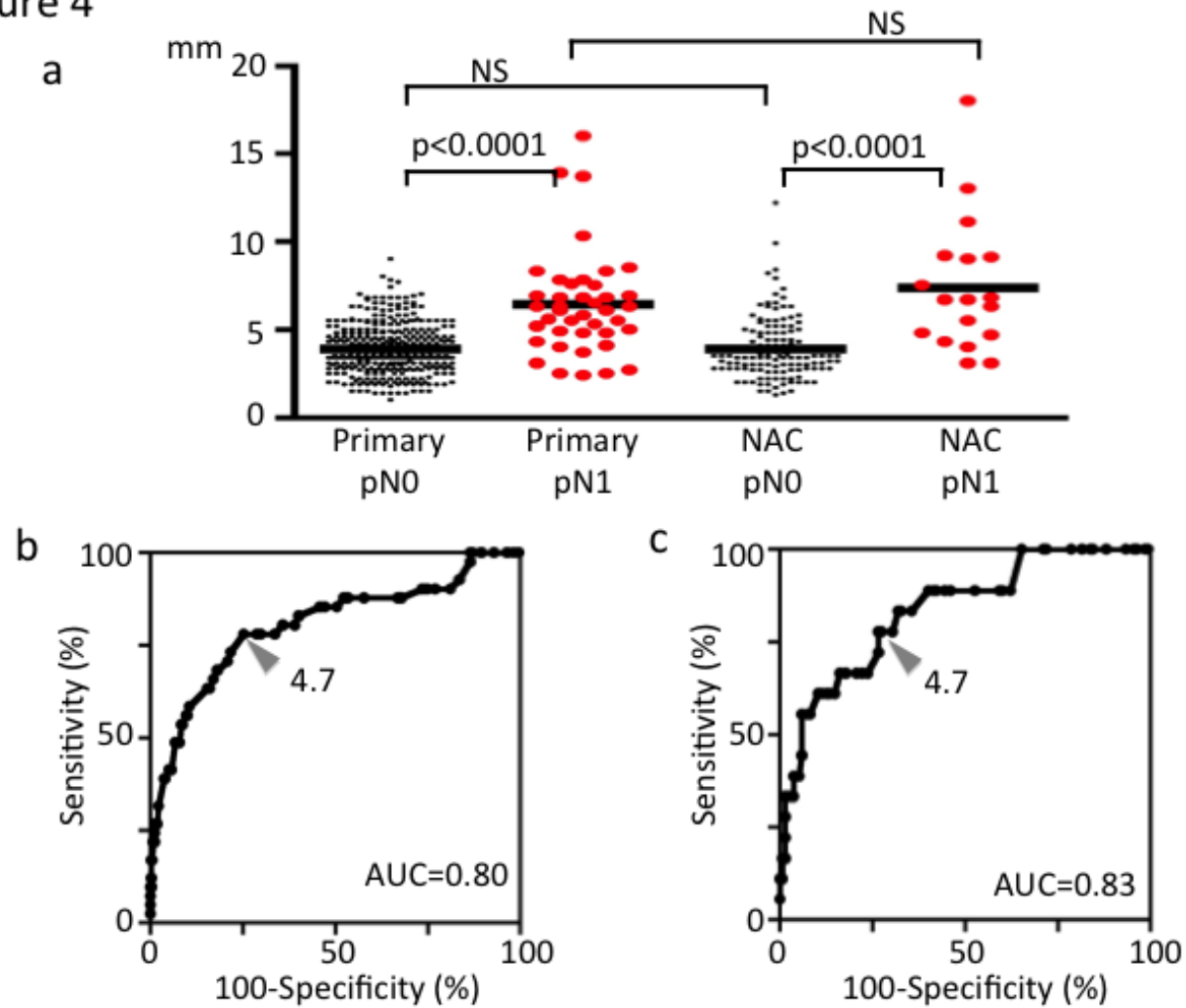
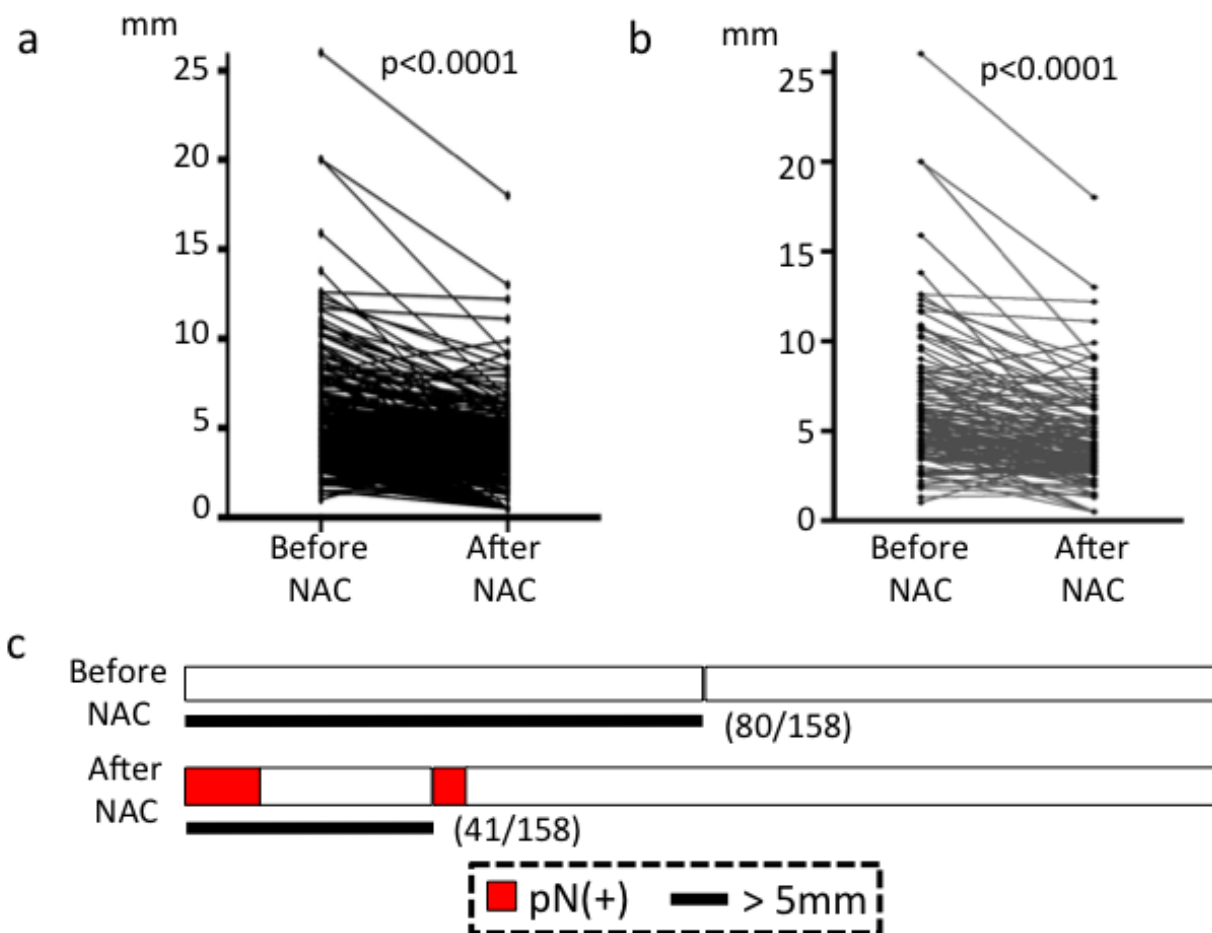


Figure 5



## Supplementary Text

### Historical analysis of the effect of NAC in eradicating LN metastases

#### MATERIALS AND METHODS

##### *Patients*

With the written consent of each patient and the approval of our ethics committee, we retrospectively reviewed the medical records of 296 cervical cancer cases (stage IA, IB, and IIB) who underwent systematic lymphadenectomy at our department between 1999 and 2011. The median number of resected pelvic lymph nodes was  $44 \pm 38$  (mean  $\pm$  2SD) per patient. A total of 199 were diagnosed with SCC and 97 with non-SCC (adenocarcinoma, adenosquamous carcinoma, etc.) (Supplementary Table 1).

##### *NAC regimen and indication*

NAC regimens are shown in Supplementary table 2. Between 1999 and 2006, the most frequently used regimen was transarterial infusion of cisplatin (CDDP), (100 mg/m<sup>2</sup>), pirarubicin (THP), (25 mg/m<sup>2</sup>), and mitomycin-C (MMC), (20 mg/patient)



every 28 days. Between 2007 and 2011, intravenous infusion of irinotecan (CPT-11), (60 mg/m<sup>2</sup> on days 1 and 8) and nedaplatin (NDP), (80 mg/m<sup>2</sup> on day 1) every 21 days was most frequently used. In principle, we conducted 2 cycles of NAC.

Because squamous cell carcinoma (SCC) was more sensitive than adenocarcinoma to chemotherapy in our preliminary analysis, we administered NAC primarily in SCC cases. As a result, most NAC cases (57/63) were SCC. From 1999 to 2011, for most stage IIB SCC patients, we administered NAC before operation. For stage IB2/IIA SCC patients, until 2006, we administered NAC for only those who had very bulky tumours, and most cases underwent primary operation. In 2007, we changed our policy and have therefore administered NAC for most IB2/IIA SCC cases. As a result, the proportion of stage IB2/IIA patients who received NAC increased significantly from 4/29 (14% through 2006) to 10/17 (59%, 2007 onward) (supplementary Figure 2a). Therefore, the primary operation and NAC were comparable among IB2/IIA cases.

### *Statistical methods*

To analyse the distribution in a 2x2 table, Fisher's exact test was employed. To analyse the distribution in a larger table, the chi-square test was used. We considered  $p < 0.05$  a significant difference.

## RESULTS

Of 296 patients receiving lymphadenectomy from 1999 to 2011, 63 received NAC. Response rate (complete response or partial response) of NAC was 91% (52/57). Because we changed our treatment policy for stage IB2/IIA SCC cases in 2007, we compared the rate of pathologically positive LN metastases in stage IB2/IIA SCC cases between the period of 1999-2006 and the period of 2007-2011. The rate of LN metastasis decreased from 41% (12/29, through 2006) to 24% (4/17, 2007 onward), although this difference was not statistically significant. Dividing all IB2/IIA SCC cases into NAC and primary surgery groups, the LN metastasis rate was significantly lower in NAC than in the primary surgery group (1/14, 7% vs 15/32, 47%) ( $p=0.02$ ) (Supplementary Figure 2b). The overall survival rate of IB2/IIA SCC patients who received NAC was better than primary operation cases (Supplementary Figure 2c).

## SUPPLEMENTARY TABLE

Supplementary Table 1: Number of patients receiving lymphadenectomy from 1999 to 2011.

Stage	SCC	Non-SCC	Total
IA	14	7	21
IB1	87	56(1)	141(1)
IB2	28(11)	18(1)	46(12)
IIA	16(2)	4(1)	20(3)
IIB	54(43)	12(4)	66(47)
Total	199(56)	97(7)	296 (63)

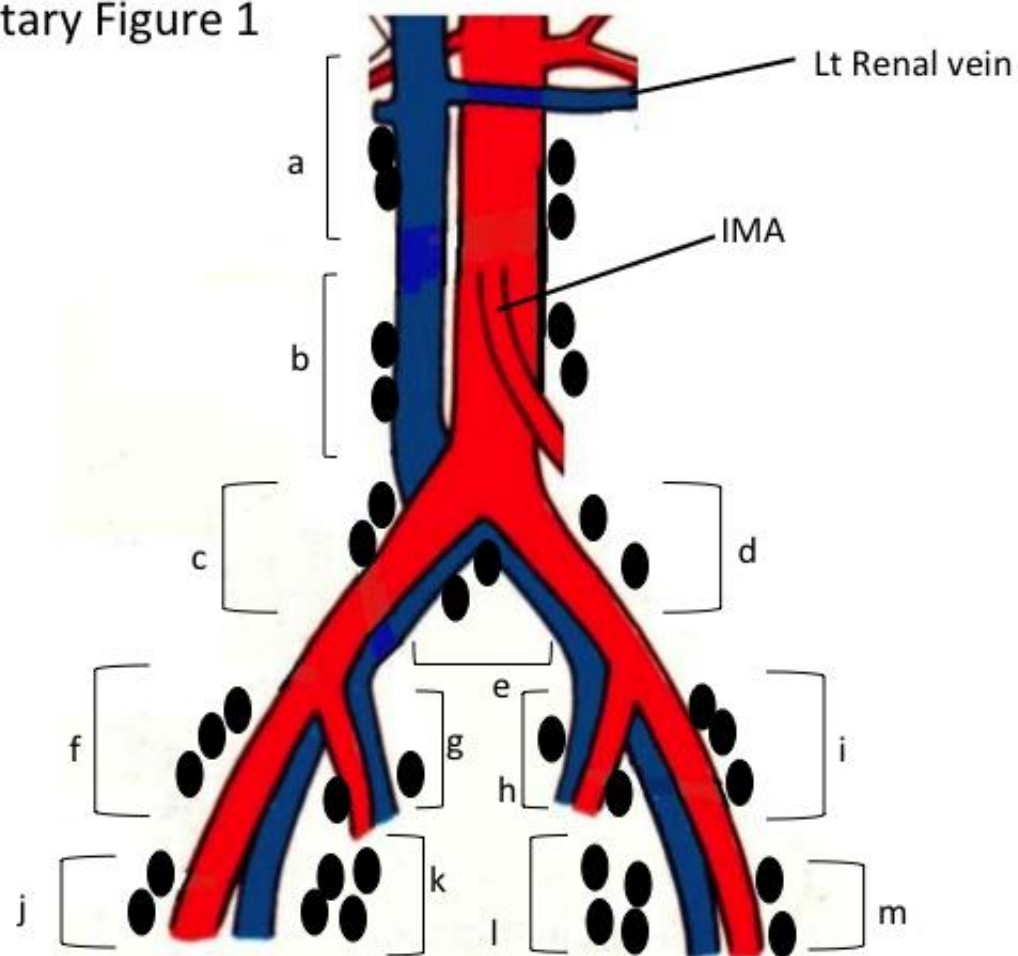
( ); NAC cases.

Supplementary Table 2: NAC regimen. Numbers of patients are shown in the table.

	stage IB2	stage IIA	stage IIB	Total
CPT-11/NDP	9	0	22	31
CDDP/THP/MMC *	2	2	15	19
NDP/Peplomycin/Ifomide	1	1	4	6
CPT-11/CDDP	1	0	1	2
Taxol/Carboplatin	0	0	4	4
Docetaxel/Carboplatin	0	0	1	1

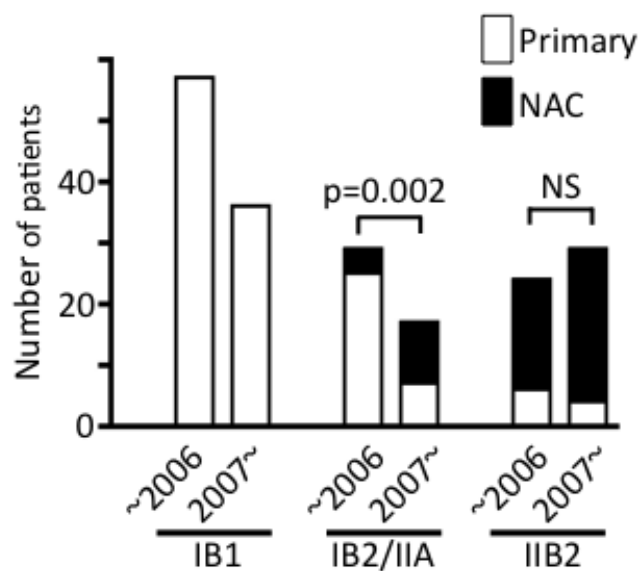
\*Transarterial infusion.

Supplementary Figure 1

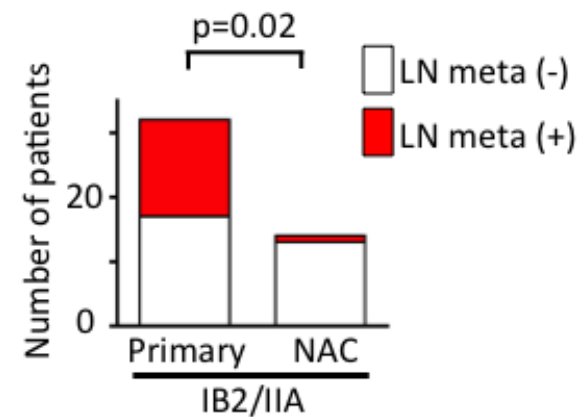


## Supplementary Figure 2

a



b



c

